DETAILED ACTION

Status of the Application

[1] A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/14/09 has been entered.

[2] Claims 22-24, 30-33, and 35 are pending in the application.

[3] Applicant's amendment to the claims, filed on 12/14/09, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[4] Applicant's remarks filed on 12/14/09 in response to the advisory action mailed on 12/8/09 have been fully considered and are deemed to be persuasive to overcome at least one of the rejections and/or objections previously applied. Rejections and/or objections previously applied to claims 1, 7-14, 21, 25-28, and 34 are withdrawn solely in view of the instant amendment to cancel these claims.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Claim Objections

[6] Claims 22-24 and 30-31 are newly objected to in the recitation of "Bn is 1-15 codons, when n is an integer from 1 to 15, or a chemical bond, when n=0;" and in order

to improve claim form and consistency, it is suggested that the noted phrase be amended to recite, *e.g.,* "B_n is a chemical bond or a codon, wherein n=0-15 and B_n is a chemical bond when n=0 or B_n is 1-15 codons when n=1-15, respectively;".

[7] Claims 22-24 and 30 are newly objected to in the recitation of "Asm is a chemical bond, when m=0, or 1-10 codons, when m is an integer from 1 to 10;" and in order to improve claim form and consistency, it is suggested that the noted phrase be amended to recite, *e.g.,* "As_m is a chemical bond or a codon, wherein m=0-10 and As_m is a chemical bond when m=0 or As_m is 1-10 codons when m=1-10, respectively;".

[8] Claims 22-24 and 30 are newly objected to in the recitation of "as part of the host cell chromosome,...extra-chromosomally to form the fusion protein...of a cell culture" and in order to improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.* "wherein the host cell comprises the nucleic acid as part of the host cell chromosome,... extra-chromosomally, wherein expressing the nucleic acid in the host cell results in formation of the fusion protein in a fermentation supernatant of a culture of the host cell".

[9] Claim 23 is newly objected to as reciting a first method step, *i.e.,* "expressing the nucleic acid", yet the remaining method steps, *i.e.,* "separating", "culturing", etc., are denoted as (A), (B), etc. In order to improve claim form, it is suggested that the *first* method step be labeled as "(A)" with subsequent steps labeled as "(B)", "(C)", etc.

[10] Claim 31 is newly objected to in the recitation of "R is an arginine codon or a chemical bond" in order to improve claim form, it is suggested that the noted phrase be replaced with, *e.g.,* "R in (ZR) is an arginine codon or a chemical bond".

[11] Claim 32 is newly objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 31 limits "(AsmR) to being "an arginine codon". Claim 32, which is dependent from claim 31, recites "(AsmR)...encodes SEQ ID NO:12 (Gly-Asn-Ser-Ala-Arg)" and thus does not further limit claim 31.

[12] Claims 31-33 are newly objected to in the recitation of "(AsmR), taken together, is an arginine codon", "(AsmR), taken together, encodes", and "(AsmR), taken together, is either", respectively. In order to improve claim form, it is suggested that the noted phrases be amended to recite, *e.g.,* "(AsmR) is an arginine codon;", "(AsmR) encodes", and "(AsmR) is either", respectively.

[13] Claim 33 is newly objected to in the recitation of "Sx is an a factor" and in order to improve claim form, it is suggested that the noted phrase be amended to recite, *e.g.,* "Sx is an α factor" or "Sx is an alpha factor", *i.e.,* replacing "a" with the symbol for alpha or with the recitation of "alpha".

[14] Claim 35 is newly objected to in the recitation of "lepirudin which has been prepared recombinantly" and in order to improve claim form, it is suggested that, *e.g.,* "which has been prepared recombinantly" be deleted from the noted phrase.

Claim Rejections - 35 USC § 112, Second Paragraph

[15] Claims 22-24 and 30 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22-24 and 30 recite the limitation "…the nucleic acid of a host cell…" There is insufficient antecedent basis for this limitation in the claims. In the interest of compact prosecution, it is suggested that applicant replace the phrase "expressing the nucleic acid of a host cell comprising: a nucleic acid sequence comprising:" with, *e.g.,* "culturing a host cell comprising a nucleic acid, the nucleic acid comprising:".

[16] Claims 32-33 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 limits "(AsmR) to being "an arginine codon". Claims 32 and 33 are dependent from claim 31, and are confusing in the recitation of "(AsmR)...encodes SEQ ID NO:12 (Gly-Asn-Ser-Ala-Arg)" and "(AsmR)…encodes SEQ ID NO:12". It is suggested that applicant clarify the meaning of the claims.

Claim Rejections – Double Patenting

[17] Claims 22-24, 30-31, and 35 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 11-12, 15, and 17 of US Patent 7,202,059 B2 (hereafter "'059 patent") in view of Dörschug et al. (US Patent 6,875,589) and Schmid et al. (US Patent 5,919,895), where both

Dörschug et al. and Schmid et al. are cited in the PTO-892 mailed on 12/12/08. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The differences between the claims 2, 11-12, and 17 of the ‘059 patent and claims 24, 31, and 35 herein are: 1) claims 22-24, 30-31, and 35 of this application require protein(Y) to be mini-proinsulin, whereas "Y" of the '059 patent is pro-insulin or insulin; 2) claims 22-24, 30-31, and 35 of this application require a Lys or Arg codon (moiety Z) before Hir, which is not required in the claims of the '059 patent; 3) claims 22-23 of this application require adjusting the pH of the supernatant to about 2.5 to 3.5 to precipitate non-desired proteins, whereas claim 13 of the ‘059 patent recites a precipitation step, yet does not expressly recite adjusting the pH to about 2.5 to 3.5; 4) claim 24 of this application requires a “releasing” step prior to concentrating the protein encoded by Y, whereas the fermentation methods of claims 11-12 of the ‘059 patent do not require a “releasing” step prior to concentrating the protein encoded by Y; and 5) claim 30 of this application requires "releasing” by treating the fusion protein with trypsin and carboxypeptidase B.

However, upon further consideration of the claims and upon further review of the reference of Dörschug, these differences would appear to be obvious variations of the claims of the '059 patent. Regarding difference 1), Dörschug teaches mini-proinsulin is a form of pro-insulin with a shortened B or C chain and is easily converted to insulin (column 1, lines 8-34). Regarding difference 2), Schmid teaches the advantage of placing an Arg at the N-terminus of a recombinantly expressed hirudin allows for removal of a fused signal sequence with trypsin (column 2, line 66 to column 3, line 1). Regarding difference 3), Dörschug teaches precipitating undesired elements from the supernatant by adjusting the pH to 3.5 (column 8, lines 4-6; column 10, lines 61-65). Regarding difference 4), claim 17 of the '059 patent expressly recites a "releasing" step prior to isolating insulin. Regarding difference 5), Dörschug teaches preparation of insulin from mini-pro-insulin using a combination of trypsin and carboxypeptidase B (column 12, lines 11-22).

Therefore, it would have been obvious to modify the nucleic acid of the '059 patent to: 1) encode Arg at the N-terminus of Hir; 2) for "Y" to be mini-proinsulin; 3) adjust the pH of the supernatant to 3.5; 4) to release mini-proinsulin prior to concentrating by enzymatic or chemical cleavage; and 5) treating mini-proinsulin with trypsin and carboxypeptidase B for conversion to insulin. One would have been motivated to make such modifications in order to: 1) allow cleavage of the hirudin moiety from the signal sequence as taught by Schmid; 2) because mini-proinsulin is an art-recognized form of proinsulin as taught by Dörschug; 3) to remove undesired elements from the supernatant as taught by Dörschug; 4) release the elements of the

fusion protein as recited in claim 17; and 5) to convert mini-proinsulin to insulin as taught by Dörschug, respectively.

[18] As noted above, the limitations of claim 32 are excluded by claim 31, which requires (AsmR) to be "an arginine codon". However, to the extent claim 32 recites (AsmR) encodes SEQ ID NO:12, *i.e.,* Gly-Asn-Ser-Ala-Arg, claim 32 is newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of the '059 patent in view of Dörschug and Schmid. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The difference between claim 2 of the '059 patent and claim 32 herein is: 1) claim 32 of this application requires protein(Y) to be mini-proinsulin, whereas "Y" of the '059 patent is pro-insulin or insulin; 2) claim 32 of this application requires a Lys or Arg codon (moiety Z) before Hir, which is not required in the claims of the '059 patent; and 3) claim 32 requires a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and protein Y moieties.

Differences 1) and 2) are addressed above. Regarding difference 3), claim 32 cannot be considered patentably distinct over claim 2 of the '059 patent when there is a specifically disclosed embodiment in the '059 patent that supports claim 2 of the patent and falls within the scope of claim 32 herein because it would have been obvious to one of ordinary skill in the art to include a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and protein Y moieties by selecting a specifically disclosed embodiment that supports that claim. See, *e.g.,* column 7, lines 62-64, which discloses a nucleic acid encoding a hirudin-proinsulin fusion protein with a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and proinsulin. One of ordinary skill in the art would have been motivated to include a sequence encoding Gly-Asn-Ser-Ala-Arg between the sequences encoding hirudin and protein Y moieties because that embodiment is disclosed as a working example within claim 2 of the '059 patent.

[19] Claims 31 and 35 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of US Patent 7,638,618 B2 (hereafter "'618 patent"). An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645

(Fed. Cir. 1985). Upon further consideration, it is noted that in view of the recitation of the transitional phrase "comprising" in claim 31, each of the individual moieties of the nucleic acid of claim 31, *i.e.,* Px, Sx, etc., can include additional unrecited elements. The conflicting claims are not identical because the nucleic acid of the '618 patent requires two codons encoding either Arg or Lys upstream of the Hir encoding nucleic acid, whereas the nucleic acid of claim 31 herein requires only a single codon encoding Arg or Lys. However, in view of the transitional phrase "comprising" in claim 31 herein, the conflicting claims are not patentably distinct from each other because claim 1 of the '618 patent anticipates claims 31 and 35 of this application when Z_1 or Z_2 of claim 1 the '618 patent is a codon for arginine.

[20] Claims 22-24 and 30 are newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 4 and 7-8 of the '618 patent in view of Dörschug et al. (US Patent 6,875,589), where both Dörschug et al. is cited in the PTO-892 mailed on 12/12/08. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The difference between the

claims 4 and 7-8 of the '618 patent and claims 22-24 and 30 herein is claims 22-24 and 30 are drawn to methods of producing a fusion protein using a nucleic acid, whereas claims 4 and 7-8 of the '618 patent are drawn to host cells comprising a nucleic acid.

However, based on the teachings of Dörschug, this difference would appear to be an obvious variation. Dörschug teaches fermentation of a host cell comprising an expression vector encoding a fusion protein comprising mini-proinsulin (*e.g.,* column 7, Example 3); teaches precipitating undesired elements from the supernatant by adjusting the pH to 3.5 (column 8, lines 4-6; column 10, lines 61-65); teaches "releasing" prior to isolating mini-proinsulin (column 2) and teaches preparation of insulin from mini-pro-insulin using a combination of trypsin and carboxypeptidase B (column 12, lines 11-22).

Therefore, it would have been obvious to use the host cell of claims 4 and 7-8 of the '618 patent to fermentatively produce a hirudin-mini-proinsulin fusion protein according to the methods of Dörschug. One would have been motivated and would have had a reasonable expectation for doing this because of the teachings of Dörschug.

[21] Claim 33 is newly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of the '618 patent. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. The difference between claim 1 of the '618 patent and claim 33 herein is that claim 33 requires Px to be a yeast ADH2 promoter and Sx to be an alpha factor leader sequence.

Claim 33 cannot be considered patentably distinct over claim 1 of the '618 patent when there is a specifically disclosed embodiment in the '618 patent that supports claim 1 of the patent and falls within the scope of claim 33 herein because it would have been obvious to one of ordinary skill in the art to include a yeast ADH2 promoter sequence as Px and an alpha factor leader sequence as Sx in claim 1 of the '618 patent by selecting a specifically disclosed embodiment that supports that claim. See, *e.g.,* column 6, lines 32-35, which discloses a nucleic acid encoding a hirudin-miniproinsulin fusion protein with a yeast ADH2 promoter sequence and an alpha factor leader sequence. One of ordinary skill in the art would have been motivated to include a yeast ADH2 promoter sequence and an alpha factor leader sequence because that embodiment is disclosed as a working example within claim 1 of the '618 patent.

Conclusion

[22] Status of the claims:

- Claims 22-24, 30-33, and 35 are pending.
- Claims 22-24, 30-33, and 35 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656